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THE EFFECTS OF THYROID FEEDING
ON THE HEART RATE IN NORMAL
DOGS AND IN DOGS WITH COM-
PLETELY DENERVATED HEARTS

A DISSERTATION SUBMITTED TO THE DIVISION
OF THE BIOLOGICAL SCIENCES IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY
1933

By
MARGARET DAY McINTYRE

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THE EFFECTS OF THYROID FEEDING ON THE HEART RATE IN NORMAL DOGS AND IN DOGS WITH COMPLETELY DENERVATED HEARTS

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From the Physiological Laboratory of the University of Chicago

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This work has been conducted to investigate the rôle of the extrinsic cardiac nerves in the tachycardia resulting from thyroid feeding in dogs. The literature on the problem is not extensive and may be divided into two main classes.

I. Acute experiments: a, experiments dealing with the effects of thyroxine on the perfused frog heart; b, experiments on the anesthetized dog studying the effect of the "thyroid hormone" on the heart rate.

II. Chronic experiments: The effect of feeding thyroid substances to normal animals and to animals with denervated hearts.

I. Experiments by Kalnis (1) on the perfused frog heart, using different concentrations of thyroxine, demonstrated that the effect of adrenaline could not be increased by previous perfusion by thyroxine. He also noted a slightly slower heart rate and an increased amplitude of beat under thyroxine perfusion. He concluded that there was no evidence to show stimulation of the sympathetic system by thyroxine.

Waldenstrom (2) studied the effect of thyroxine on vagus action in the perfused frog heart. He reports that in no case did the addition of thyroxine modify the vagus inhibition.

Cannon (3) using the denervated heart of the anesthetized cat reported an increase in heart rate following massage of the thyroid gland, and also on stimulation of the cervical sympathetic. This effect was noticed after a delay of from 30 to 60 minutes. The reason for this effect is not clear, as it has not been conclusively shown that there is a definite increase in secretion of the thyroid gland during such procedures. Carlson and Hektoen (4) have shown that there is no demonstrable increase in the production of thyroglobulin, as tested by the precipitin reaction either on stimulation of the sympathetic fibers to the gland or on massage. Van Dyke (5) found no change in the iodine content of the gland on stimulation of the cervical sympathetic. Smith and Couta-Silva (6) found no increase in basal metabolism of dogs after massage of the thyroid gland. Kunde (7) has shown that there is no observable effect on the heart rate for at least

ten hours following the injection of thyroxine or after feeding dried thyroid gland. This was true also in the thyroidectomized dog. II. Enderlen and Bohnenkamp (8) have conducted a series of experiments on thyroid feeding in normal dogs and in dogs with denervated hearts. Dogs were subjected to the Friedenthal operation in which the vagi are sectioned in the chest and the upper thoracic sympathetic chains are removed. Five grams of Merck's thyroid were fed daily to a group of normal and operated animals. At the beginning of the experiment the dogs weighed from 15 to 18 kilograms, thus making the daily dose of thyroid around 0.3 gram per kilogram of body weight. The feeding covered a period of from seven to eight weeks, during which time the control animals lost weight, showed auricular flutter and died, while the operated animals showed no heart changes and gained from one to three kilograms. They concluded that thyroid substances act on the heart only by way of the cardiac nerves. The early death of the normal dogs fed this dose of thyroid as well as the gain in weight in the heart denervated dogs on the same dose is contrary to the experience of this laboratory.

The following experiments have been performed in an effort to study the problem in a more extensive way. It was desirable to prepare dogs with completely denervated hearts and at the time when this phase of the work was started, it was felt that sectioning both vagi and removing the stellate ganglia would give a heart rate which would not vary except when acted upon by humoral means. Six dogs were prepared. The experimental period extended from October 20, 1929 to August 25, 1930.

Heart rates. The normal heart rate with normal variations was secured on each dog prior to operation. The animal was taught to rest quietly on a table. The pulse rate was measured by either counting the beat in the femoral artery or by means of a tambour on the apex beat. These methods gave the same results and it was felt in the later work that it was unnecessary to continue with the graphic records as they took more time than their value warranted. The rate was measured when the animal was quiet and relaxed after an initial one-half hour rest. The rate was also taken at every disturbance during the half-hour following the rest period.

Operations. Each animal was subjected to four operations: 1, right stellate ganglion; 2, left stellate ganglion; 3, right vagus; 4, left vagus. The stellate ganglion was removed by entering through the midline on the dorsal side, cutting through the rhomboids and laying back the scapula. Muscle tissue between the first and second ribs was removed and the ganglion was brought into view. It was cut free from all its connections and removed. Usually no pneumothorax occurred. If it did, all speed was made in removing the ganglion and closing the wound. The muscles were sutured and the skin wound closed. The recovery was usually good. It was found not advisable to remove both ganglia at the same time as the shock was too severe.

The original intention to cut both vagi below the origin of the recurrent laryngeal nerves from a midline neck incision was not carried out as it was suggested that all fibers might not be reached. For this reason it was necessary to enter both sides of the chest and section these nerves where all fibers could be seen. This was done under artificial respiration. Tracheotomy was performed as it was found that forcing a large enough tube through the larynx to get positive pressure did more damage than cannulating the trachea. The chest was entered between the third and fourth ribs and the vagus was brought into view. A section of nerve about one and one-half inches long was removed below the origin of the recurrent laryngeal nerves. The incision was closed while the lungs were filled.

RESULTS. Four out of the six dogs survived the four operations in good health. In dog I, ten days following the section of the second vagus, chronic vomiting began. The animal did not improve and was sacrificed twenty-seven days after the operation. The rate in this dog is included in the tables. The figures represent heart rates taken when the animal was normal and in good condition. The same set of effects (chronic vomiting) was seen in dog V. This dog was sacrificed seven days after the second vagus was cut. The animal was normal for three days following this operation, and so the heart rate is included for this period.

Criteria of denervation. Immediately after removal of the stellate ganglion the nictitating membrane spread over the eye. The membrane withdrew after some days except in dog I where it persisted over the right eye from October 25, 1929 to July 1, 1930. If no cardiac slowing was obtained on electrical stimulation of the vagus at the level of the inferior cervical ganglion, it was inferred that all vagus fibers to the heart had been sectioned.

At the end of the experiment these animals were injected with atropine (3 mgm.). All showed cardiac acceleration. It was thought that vagus regeneration had taken place, but on electrical stimulation of the vagus under anesthesia, only one vagus in one dog (dog III) was found to have functionally regenerated and on autopsy this was confirmed macroscopically. The other dogs showed no evidence of vagus or sympathetic regeneration.

The acceleration of the denervated heart after injection of atropine has been observed by several workers. Enderlen and Bohnenkamp (8) described acceleratory effects which they attributed to the "intracellular" action of the drug. Dresbach and Waddell (9) obtained acceleration in the heart rate of the cat in which the extrinsic cardiac nerves had been cut. Acceleration of the heart rate in the animal with both vagi cut following the injection of atropine has been described in the dog by Rogers (10) and in the cat by Cannon (11). Carlson (12) described a stimulation of the heart ganglion in *limulus* upon the addition of atropine to the ganglion.

In table 1 are represented the changes in heart rate following the different operations. Basal heart rate represents that heart rate obtained after one-half hour rest, during which time there had been no disturbances. "Maximal variations" represent the greatest variations occurring during the following one-half hour rest period due to such factors as wagging the tail, moving the head, etc., etc. Each figure represents an average of twenty counts on successive days unless otherwise indicated (*).

It was felt that since the heart still accelerated on slight movements, all the extrinsic cardiac fibers had not been removed. Stellatectomy and

TABLE 1
Average heart rates before and following the different operations

DOG	PERIOD OF EXPERIMENT	NORMAL		AFTER EXTIRPATION OF STELLATE GANGLIA		AFTER SECTION OF CARDIAC VAGI	
		Basal heart rate	Variations	Basal heart rate	Variations	Basal heart rate	Variations
I	October 25, 1929 July 1, 1930	73	+23	70	+24	70	+23
II	November 14, 1929 August 21, 1930	92	+34	91	+30	90	+29
III	November 20, 1929 August 21, 1930	84	+28	80	+26	80	+27
IV	November 25, 1929 August 25, 1930	88	+14	86	+15	85	+14
V	November 30, 1929 February 15, 1930	70	+20	71	+20	68	+20
VI	December 2, 1929 August 24, 1930	74	+18	72	+14	73	+15

vagotomy had been complete in these animals. Cannon (13) has described in the cat sympathetic fibers which leave the thoracic chain as low as the fifth or sixth ganglion and pass directly to the heart. Dresbach and Waddell (9) confirm these findings. Perman (14) has demonstrated similar findings in the calf. The author made careful dissections in ten dogs and in six very fine fibers were seen leaving the sympathetic chain as far down as the sixth thoracic ganglion. These could not in all cases be traced the entire way to the heart, but their general direction indicated the heart as a possible destination. In three of the dogs the fibers were traced to the aorta.

It was thought desirable to prepare a series of animals in which the entire

thoracic sympathetic chains were removed and the vagi sectioned. The splanchnics were cut in order to denervate the adrenals, thus lessening any heart effects due to this factor. The abdominal sympathetic chains were removed for the same reason.

Operations. Three operations were required. The work was done under ether anesthesia, using a modified Meltzer tracheal insufflation apparatus (15). Compressed air was led through an ordinary ether bottle and by means of a small rubber catheter to the bifurcation of the trachea. To obtain positive pressure a Kunde mask was placed over the snout. In the mask was an inlet carrying the catheter and an outlet carrying the expired air down a tube into a water bottle. By raising or lowering the tube in the water the lungs could be inflated or deflated as desired. The lungs were partially distended throughout the operation. Respiratory exchanges seemed normal in all the dogs operated. The administration of ether was smooth and easily regulated.

The normal basal heart rate was obtained and then the animal was subjected to the three operations. Four dogs survived these procedures in good health. Two dogs of approximately the same weight and age were chosen as controls for the adult dogs and one litter mate for the puppy studied. Small dogs were chosen as it was found that the thoracic sympathetic chain could thus be removed through one incision.

Operation I. The right thoracic sympathetic was removed from the stellate ganglion to the diaphragm. The right vagus was sectioned below the origin of the recurrent laryngeal nerve. Any fibers running from the recurrent to the heart were sectioned. The right splanchnic was cut. The vessels above the heart were stripped to remove as much of the nerve net as possible.

Operation II. The left thoracic sympathetic was removed from the stellate ganglion to the diaphragm. The left vagus was dissected free from the connective tissue surrounding it and all thoracic branches were cut, thus leaving the vagus to the gut intact. The left recurrent laryngeal was cut, but with the right intact the animal suffers no ill effects. The vessels above the heart were stripped.

Operation III. The abdominal sympathetic chains were removed and the splanchnics again sectioned. These operations were carried out as described with the following exceptions. In dog V the left splanchnics could not be reached in the chest and since it is not possible to reach all fibers in the abdomen the left adrenal was removed. In dog VI, the entire left vagus was cut at the level of the aorta.

Criteria of the effectiveness of heart denervation were: 1. Nictitating membrane drawn over the eye immediately after operation. 2. No cardiac slowing when the vagi in the neck were electrically stimulated. 3. A steady heart rate after one-half hour rest which did not vary when the

animal moved slightly. In control animals, the slightest movement always gave a greatly accelerated heart rate.

Heart rates. The heart rate was taken after one half-hour of rest. After again taking the rate at forty minutes, the animal was disturbed in some way and the rate again taken.

Basal metabolic tests. On two dogs, one operated (dog V) and one control (dog I) basal metabolism tests were run. This was done in order to measure the effectiveness of the thyroid dosage. These tests were run eighteen hours after feeding, and after an initial half-hour rest.

Thyroid dosage. After a control period had been run on each dog, thyroid feeding was begun, giving each dog 0.6 gram per kilo per day. Armour's thyroid was used. The thyroid mixed with milk was fed before the regular food was given. All dogs seemed fond of the mixture. The cages were watched to see whether any was lost in vomiting. This did not occur.

TABLE 2

DOG NUMBER	AVERAGE BASAL HEART RATE DURING TWO WEEK CONTROL PERIOD	EFFECTS OF SLIGHT MOVEMENTS
<i>Control dogs</i>		
I	74	+31
II	77	+18
IX	92	+33
<i>Operated dogs</i>		
V	57	+2
VI	68	+1
VII	66	+2
X	82	+1

Diet. The dogs were kept in a constant diet throughout the experimental period. Enough food was given to maintain a constant body weight under normal conditions. During thyroid administration the same amount of food was fed. In the case of the two puppies, the normal diet was fed ad libitum. The diet consisted of:

Ground meat.....	50 per cent
Bread.....	25 per cent
Milk.....	25 per cent
Bone meal.....	

Electrocardiograms. On all dogs studied, electrocardiograms were run weekly before and during thyroid feeding. In the tracings the following measurements were made: 1, duration of P wave; 2, direction and height of P wave; 3, P-R interval; 4, direction, normality and height of R wave; 5, duration of QRS; 6, direction and height of T wave; 7, QRS-T (systole).

Results. 1. In the animals subjected to the second series of experiments, immediate acceleration in the heart rate following slight movements was practically abolished (see table 2).

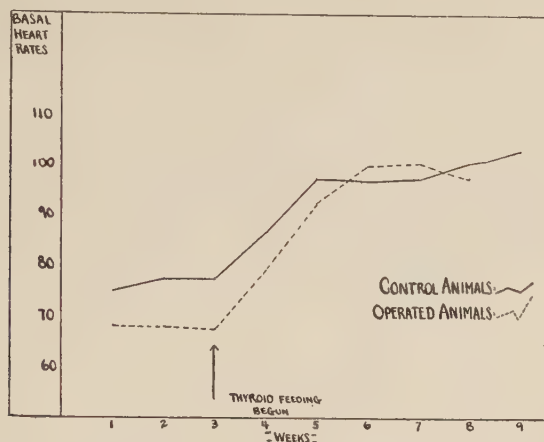


Chart 1. Average weekly heart rates in the control and operated groups before and during thyroid feeding.

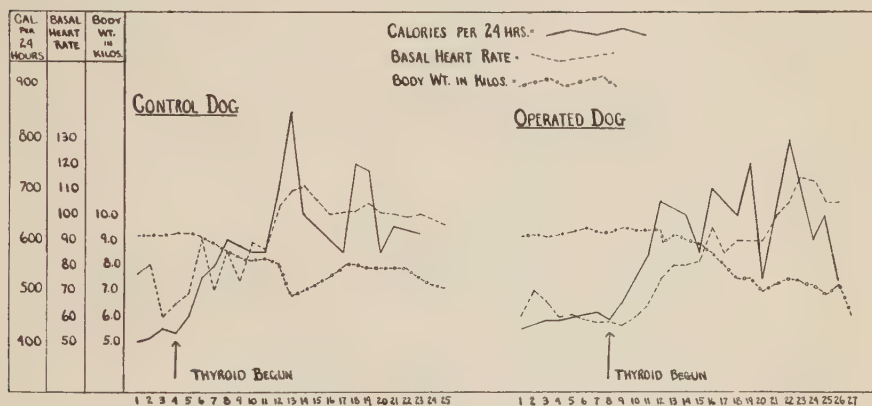


Chart 2. Variation in basal heart rate, basal metabolic rate and body weight before and during thyroid feeding. Small figures at bottom of chart indicated three day intervals.

2. Effects of more extensive movements and exercise, such as running, etc., were not studied. It was noticed that these hearts accelerated after the ingestion of food.

3. The basal heart rate was lower (5-10 beats) following heart denervation.

4. Dog VI was the only dog in the series which showed erection of the hairs in fighting. This disappeared after sympathectomy.

5. In all the operated dogs and in two of the controls, the vagi were stimulated aseptically before the experimental period was begun. No cardiac slowing was observed in the operated dogs. In the control animals complete cardiac inhibition was seen lasting from three to five seconds.

6. In all the animals of the second group, operated and controls, the basal heart rate was considerably increased during thyroid feeding (see chart 1).

7. In those animals on which metabolism tests were run the basal heart rate was found to vary with the basal metabolic rate (see chart 2).

8. All animals lost weight during thyroid administration.

The following gives the maximum loss of weight in each dog:

DOG NUMBER	CONTROL DOGS	DOG NUMBER	OPERATED DOGS
	<i>per cent</i>		<i>per cent</i>
I	25	V	33
II	45	VI	30
IX (puppy)	13	VII	32
		X (puppy)	7

9. There were no marked differences in the electrocardiograms of the normal and operated dogs. Table 3 gives a summary of the measurements made before and during thyroid administration. The main differences, it will be seen, are those accompanying a faster heart rate. In the control dogs the T wave became larger during thyroid feeding. This is a usual accompaniment of hyperthyroidism in man. In the operated dogs, this difference in the T wave was not noticeable. In dogs V and VI, the T wave was 1.5 and 1.0 less than during the control period.

10. All animals were in good health before the experimental period began. There was little, if any, difference in the behavior of the control and operated dogs, prior to the thyroid feeding period. During the thyroid period, the operated animals became weak and unable to run about. The control dogs remained lively until the end of the experiment. The appetites in all the dogs remained excellent throughout the period.

11. Three of the operated dogs died after from four to seven weeks on thyroid feeding.

Chronic vomiting in dog VI (beginning two weeks after thyroid administration was started) led to pneumonia and death.

Dog X died of pulmonary embolism.

Dog V became weak and died. No pathology was found.

Only one control dog died during the experimental period. The death was similar to that observed in dog V. Both dogs were extremely emaciated. The other dogs, I, IX and VII were killed by ether after taking electro-cardiograms before and during vagus stimulation. The control dogs

showed typical cardiac inhibition. A slight effect was seen on stimulation of one vagus in the operated dog. Autopsy in all of the operated dogs revealed no regeneration of either sympathetic or vagus fibers, except in dog VII, where some fibers leaving the left vagus were seen coursing toward the heart.

TABLE 3

Showing the averages of the measurements made on the electrocardiographic tracings before and during thyroid administration

DOG NUMBER	DURATION OF P WAVE	HEIGHT OF P WAVE	P ^c -RINT.	HEIGHT OF R WAVE	DURATION OF QRS	HEIGHT OF T WAVE	QRS-T	ABNORMALITIES
	sec- onds	mm.	sec- onds	mm.	sec- onds	mm.	sec- onds	
I. Control period....	0.04	3.0	0.15	14.0	0.045	3.0	0.22	None
Thyroid.....	0.14	3.9	0.12	14.0	0.041	7.1	0.24	Few extra P waves
II. Control period...	0.032	2.1	0.106	14.0	0.044	2.5	0.24	None
Thyroid.....	0.032	2.6	0.98	16.7	0.041	5.0	0.26	Few extra P waves
V.* Control period...	0.052	2.8	0.130	21.3	0.045	5.1	0.23	None
Thyroid.....	0.040	3.2	0.108	19.4	0.045	3.6	0.25	None
VI.* Control period...	0.052	3.0	0.12	11.5	0.046	3.5	0.25	None
Thyroid.....	0.040	3.3	0.114	10.3	0.042	2.5	0.253	None
VII.* Control period..	0.052	2.3	0.100	14.5	0.040	4.0	0.255	None
Thyroid.....	0.040	4.7	0.104	9.6	0.046	5.6	0.26	None
IX. Control period..	0.044	2.93	0.114	15.1	0.058	4.6	0.233	None
Thyroid.....	0.038	2.83	0.99	19.1	0.040	6.6	0.249	None
X.* Control period..	0.056	2.45	0.12	16.5	0.040	3.25	0.21	Few extra P waves
Thyroid.....	0.040	3.0	0.112	11.0	0.038	4.0	0.23	Few extra P waves

* = operated dogs.

DISCUSSION. The work on the denervation of the dog heart confirms Cannon's findings (13) in the cat. The heart rate in dogs after complete sympathectomy and vagotomy is different from that in dogs in which vagotomy and removal of the stellate ganglia had been performed in that quick acceleration due to slight movements was not seen in the dogs with completely denervated hearts.

There was no marked difference in the response of the heart in the operated and control animals to thyroid administration. This work therefore

clarifies the problem of the mechanism of the tachycardia of hyperthyroidism to the extent that the thyroid action is not primarily via the extrinsic cardiac nerves.

The findings of Enderlen and Bohnenkamp (8) of auricular flutter and death in the control animals, and no effect on the operated animals, are not confirmed. No true auricular flutter was seen in any of these animals. It might be argued that the experiments did not extend over a long enough period. Two dogs were fed the described dose for over eight weeks. The rest of the series varied from four to seven weeks. This period is comparable to that described by the above authors. The dosage used was twice that used by these workers.

CONCLUSIONS

1. The heart rate in the dog with complete cardiac denervation does not change in response to slight movements. This is not the case when vagotomy and removal of the stellate ganglia are performed.

2. The tachycardia of chronic experimental hyperthyroidism is practically identical in dogs with complete heart denervation and in dogs with all the cardiac nerves intact.

3. The rate of loss of body weight and temperature elevation on comparable doses of thyroid hormone is the same in the normal and in the heart denervated dogs, but the latter animals are more incapacitated (asthenia) by the hyperthyroidism.

The author wishes to express her appreciation of Mr. Edward Wallace's assistance in the electrocardiographic work and her thanks for the advice of Dr. A. J. Carlson throughout the course of the experiments.

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